AD_____

Award Number: DAMD17-02-1-0040

TITLE: Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer

PRINCIPAL INVESTIGATOR: James P. Grigsby, Ph.D.

CONTRACTING ORGANIZATION: University of Colorado Health Sciences Center
Aurora, Colorado 80045-0508

REPORT DATE: February 2004

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	February 2004	Annual (7 Jan 2003 - 6 Jan 2004)

4. TITLE AND SUBTITLE
Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer

5. FUNDING NUMBERS
DAMD17-02-1-0040

6. AUTHOR(S)
James P. Grigsby, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Colorado Health Sciences Center
Aurora, Colorado 80045-0508

E-Mail: jim.grigsby@uchsc.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Original contains color plates: All DTIC reproductions will be in black and white.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)
The purpose of this project is to examine the nature and severity of cognitive impairments experienced by men undergoing continuous androgen deprivation or intermittent androgen deprivation treatment. The cognitive abilities of androgen deprivation patients will be compared with those of a sample of healthy men. We are undertaking collection of data from three groups: 35 men on intermittent androgen deprivation therapy, 35 men on continuous androgen deprivation therapy, and an age- and education-matched sample of 35 healthy (cancer-free) men. Our major hypothesis is the patients undergoing androgen deprivation therapy will experience impairments in those cognitive abilities reported in the research literature to be related to androgen levels (e.g., spatial ability, working memory for visual information). There are as yet no results to report. During this second project year, we have begun data collection with androgen-deprivation subjects, but have continued to spend an inordinate amount of time in obtaining necessary institutional approvals.

14. SUBJECT TERMS
Androgens, testosterone, cognition disorders, prostate cancer, quality of life

15. NUMBER OF PAGES
23

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

Introduction

Hormonal treatment of prostate cancer by means of androgen deprivation (AD) can be an effective means of inducing tumor regression and delaying progression of the disease. The treatment, however, adversely affects quality of life (QOL), causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive function also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of possible negative influences of life-prolonging treatment on their QOL, and the development of means to treat them, is of great importance. The research questions we are investigating address the relationship between sex steroid levels and different aspects of cognitive functioning. Our specific aims are to: (1) assess whether there is evidence of cognitive impairment among patients on AD therapy; (2) assess the nature and severity of that impairment; (3) determine whether any cognitive deficits observed are related to testosterone (T) suppression, decreased estrogen level, or both; (4) evaluate the relationships between performance on specific cognitive tests and levels of certain sex steroids; and (5) examine the relationship among performance on cognitive measures, steroid levels, and QOL. We are examining men on continuous AD, a matched sample of men on intermittent AD, and a matched sample of healthy controls using tests of working memory, learning, verbal fluency, spatial perception, and verbal reasoning. Each subject is tested at three time points, approximately four months apart. We obtain T and estrogen levels, evaluate cognition, and assess QOL at each time point. *(Appendix A contains the original protocol submitted to the Department of Defense and the original statement of work for the study.)*

Body of Report

After receiving approval from the University of Colorado Health Sciences Center's Institutional Review Board (COMIRB), the University's General Clinical Research Center (GCRC), and the University of Colorado Hospital's Hospital Research Resources Committee (HRRC), data collectors were trained and recruitment of subjects began in December 2002. *(The initial phases of the lengthy process of obtaining institutional approval to conduct the study were described in the first annual report, the body of which is attached in Appendix B.)* Subject enrollment was halted in late January of 2003 (Study Year 2) when we were informed that the University of Colorado Cancer Center's Protocol Review & Monitoring Committee (PRMC) would have to approve the study. This development was unexpected, as we originally had been informed that the Committee's approval was not necessary for nontherapeutic studies. The Committee's bimonthly meeting schedule and required several-week lead time for submitting an application resulted in a lengthy delay before approval was granted on July 2, 2003 *(Appendix C contains the approval form related to the PRMC application).*

During that delay, two applications for review were submitted to COMIRB. In January 2003, a protocol amendment was submitted, requesting approval of: (1) the addition of a new data collection site to the study protocol (discussed below), (2) a brief subject recruitment and eligibility form for use in screening eligible patients, (3) revisions to the recruitment advertisement, and (4) a new recruitment letter. COMIRB approval was received on February 5, 2003.

The application itself is not included as it was submitted as part of last year's annual report.) In April, we submitted our continuing review application to COMIRB, which included a request for approval of: (1) four new authorization forms required as a result of the implementation of the privacy regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996, (2) a new Patient Background and Demographic Information Form, and (3) minor revisions to other study documents. COMIRB approval was received on May 13, 2003.

At the time that PRMC approval was received, subject recruitment resumed. Recruitment letters from Dr. Glodé along with an informational flyer about the study were mailed to 116 members of the University of Colorado Hospital's Prostate Cancer Support Group and 10 additional patients from Dr. Glodé's practice. Twenty-four individuals called in requesting information about the study. Telephone screening to determine eligibility was conducted with all 22 interested patients, and five of these individuals were deemed to be ineligible for participation according to the study's inclusion and exclusion criteria. Five patients were determined to be eligible and have undergone baseline cognitive testing. One of these five patients has been seen for his first follow-up exam. The remaining 14 patients currently are "on hold." These patients are men who already were on androgen blockade when they heard of the study, and therefore did not meet the admission requirements (i.e., that they *not* be on the androgen blockade protocol at baseline). In order to obtain baseline data for these patients, it is necessary to conduct their first assessments at a time when their T levels have normalized, just prior to receiving another lupron or zoladex injection. Research project staff are following these patients closely to ensure that we will be able to identify the appropriate time to conduct their baseline assessment visits.

The enrollment of healthy control subjects is a secondary step to the enrollment of prostate cancer patients. So that we may match control group members with the cancer patients on the characteristics of age and education, we have delayed recruitment of control subjects. Now that assessment of cancer patients has begun, recruitment of controls can proceed. Enrollment of an adequate sample of healthy control subjects is not expected to be problematic. The Principal Investigator has made contacts with cancer support groups (friends and family members of support group members are likely control subjects) and a senior center, from which an adequate number of healthy controls will be available.

In the initial proposal, we indicated that we would involve subjects from other Universities, including Wayne State and the University of Washington. Our plans changed, however, when our University's GCRC refused to pay for assays conducted using blood from patients not enrolled locally. To compensate for the loss of patients from these other Universities, we have added an additional local data collection site to the study protocol. This new site, Western Urologic Research Center (WURC), is a large specialty private practice in the Denver area, which has the potential to refer a sizeable number of patients who would be eligible for enrollment and able to undergo assessment at our institution's GCRC. Patient privacy concerns have resulted in a delay in the enrollment of patients from WURC. Members of the organization expressed concern that it might be a violation of HIPAA privacy regulations for the practice to identify patients eligible for recruitment in the study. It is our position that there would be no violation of patient privacy if the organization identified and sent the study recruitment letter out to eligible patients, without providing any protected health information to our project staff. Dr. Larry Karsh, the Research Director for the practice, has indicated his commitment to participate in the study and the other five physicians are expected to follow. The decision to recruit WURC patients will be left up to individual physicians in the practice.

Key Research Accomplishments

At this time, we expect that recruitment of subjects will accelerate. The impasse with the HIPAA Compliance Committee at WURC has been resolved and we are working to recruit the support of the individual physicians in the practice. In addition, we have made contacts with two new prostate cancer support groups, both of which have expressed interest in the study. The Principal Investigator will present information about the study to both groups in March.

Reportable Outcomes

None to report.

Conclusions

No scientific conclusions to report. At this time, we expect that it will be necessary to request a no-cost extension in order to complete the study.

APPENDICES TO

ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

APPENDIX A

ORIGINAL PROTOCOL AND STATEMENT OF WORK

This appendix contains the original protocol submitted to the Department of Defense and the original statement of work for the project. They are included for reference, for the reviewer's convenience.

A. BACKGROUND

1. Introduction

We are submitting the proposed three-year study as a New Investigator Award Proposal, under the Department of Defense Congressionally Directed Medical Research Program (CDMRP) for prostate cancer. The proposed study, which is based on a sound rationale and a well-established body of literature regarding sex steroids and cognition, is relevant to the *Prostate Cancer Research Program* Fiscal Year 2001 Program Announcement insofar as the results would contribute to improvement in "the quality of life for individuals and their families living with prostate cancer" by addressing a previously neglected issue: the effects on cognition of hormone therapy for prostate cancer. We request funding for a period of 36 months.

Prostate cancer occurs chiefly in older men. It is an illness that can be cured or effectively managed in a large percentage of cases that are characterized by a relatively benign course. Even when the cancer has metastasized to distant sites, the likelihood of survival for five years or more, given proper management, can be good. Given that men with prostate cancer may require a number of years of therapy, factors influencing quality of life (QOL) are very important. Hormonal treatment of prostate cancer is widely used, and as discussed below, the suppression of endogenous sex steroids can have serious effects on physical, emotional, and cognitive well-being. The cognitive effects of hormone therapy have not previously been addressed. These effects and their implications for QOL are the focus of our study.

The proposal is a supplement to the National Cancer Institute (NCI)-funded study, *Phase III randomized study of intermittent versus constant combined androgen deprivation (Bicalutamide and Goserelin) in patients with stage IV prostate cancer responsive to such therapy*. That study carries the following protocol ID numbers: SWOG-9346, CAN-NCIC-JPR8, CLB-9594, INT-0162.

2. Prostate Cancer

When carcinoma has not spread beyond the prostate, the disease may be curable. If it has metastasized, especially to distant sites, the likelihood of mortality is high, although survival beyond five years is not unusual. A number of risk factors have been identified and survival is a function of such factors as heredity, localization of the tumor and presence of pelvic lymph node involvement, histologic grade (poorly differentiated tumors carry a worse prognosis), Gleason score, patient age, comorbidities, level of serum acid phosphatase and prostate specific antigen (PSA), diet, and DNA ploidy (Chodak et al., 1994; Gittes, 1991; Lieber, 1990; Matzkin et al., 1992; Nativ et al., 1989; Oesterling et al., 1987; Pisansky et al., 1993, 1997). The mean age of diagnosis is 72 years and the incidence of prostate cancer increases with advancing age. The primary treatment options for prostatic adenocarcinoma include surgery, radiation, and hormone therapy. Surgery (prostatectomy or cryosurgery) may be curative for men with low grade tumors, and without metastases, who are in good health (Shinohara et al., 1996; Zincke et al., 1994). Radiation therapy may be effective for patients with tumors of Grade I-III who are not candidates for surgery (Duncan et al., 1993). Both external beam radiation and interstitial implantation of radioisotopes are widely used (Ragde et al., 1997; Wallner et al., 1996). Radioisotope seeds are sometimes provided post-surgically when indicated by pathologic findings from the surgery.

3. Hormonal Treatment of Prostate Cancer

Prostate cancer tends to be androgen-dependent. That is, it grows rapidly in the presence of androgens (male hormones), but under conditions of androgen suppression, apoptosis is induced, and this leads to tumor regression. Hormonal therapy leads to reasonably good short-term management, but long-term outcomes often remain relatively unchanged as a result of androgen deprivation (AD). Over a period of time, tumors tend to become androgen-independent and growth begins to occur once again in spite of the androgen blockade. Depending on the grade and stage of tumor, as well as the age of the patient, hormone treatment may be used as an adjuvant approach. About 65% of men with distant metastases undergo hormonal therapy. Such therapies may take the form of surgical castration (orchiectomy) or the use of substances such as leuprolide or goserelin, which are luteinizing hormone releasing hormone (LHRH) agonists, and bicalutamide or flutamide, which are nonsteroidal anti-androgens. These agents block the production of testosterone (T), producing AD.

Androgen deprivation is a common approach to the treatment of Stage IV prostate cancer, sometimes using both anti-androgenic agents and LHRH agonists in what is referred to as combined androgen deprivation (CAD) therapy. However, there are two major drawbacks to AD. First, some data suggest that continuous therapy may lead to development of androgen-independent tumors. Second, the AD syndrome, which develops concomitant with this therapy, is associated with deleterious effects on QOL. For example, Herr and O'Sullivan (2000) reported that men on AD, compared with those not on AD, reported greater fatigue, greater emotional distress, and a lower QOL overall. Clark and associates (2001), in a study of 201 men treated with either chemical or surgical castration, found that among their subjects, 70% complained of hot flashes, 34% of nausea, and 81% of impotence. Other reported side effects include gynecomastia, breast tenderness, and loss of libido.

The adverse effects of continuous AD on QOL has led to the use of intermittent AD or intermittent CAD, as in the clinical trial protocol discussed above. In intermittent AD, following an induction phase of androgen blockade that reduces PSA to undetectable levels, AD therapy is discontinued. Patients then are observed until either their PSA rises or they show clinical signs of progressive disease. They then resume AD for a second round, after which time, if PSA is within normal limits, AD is again discontinued. The use of intermittent CAD as an alternative to continuous androgen suppression has been shown to improve QOL, reduce toxicity, facilitate recovery of libido and erectile functioning, and slow tumor progression toward an androgen-independent state by allowing some apoptotic recovery (Crook et al., 1999; Goldenberg et al., 1995, 1999; Higano et al., 1996; Wolff & Tunn, 2000). The NCI-funded Phase III trial, for which the proposed study is a supplement, was designed to provide data regarding the effectiveness of the continuous and intermittent approaches to CAD, with survival, PSA levels and changes, and several indices of QOL as endpoints. In this supplement, we expand the scope of QOL outcomes to include several specific aspects of cognitive functioning.

4. Sex Steroids and Cognition

In addition to findings of adverse effects reported in the literature, anecdotal reports by patients treated with continuous CAD at University of Colorado Hospital suggest that there may be a relatively high prevalence of cognitive impairment among this population. This has not previously been reported in the literature and is the focus of this proposed investigation. Our goal is to study whether it occurs, to determine the nature of such dysfunction, and to evaluate its relationship to hormonal status.

The mechanism(s) by which AD may interfere with cognitive functioning, as well as the nature of such impairment, are suggested by the scientific literature. Such effects could possibly be a result of the fatigue and dysphoric mood that often accompany AD, as either of these could disrupt the speed and capacity of information processing with consequent deleterious effects on sustained attention, learning, memory, and complex problem solving. It has been demonstrated, however, that certain sex steroids appear to have relatively direct effects on circumscribed aspects of cognition (for recent reviews see Erlanger et al., 1999; Henderson, 1997; Kimura, 1999; Sherwin, 1994a, b). Although the molecular means by which this is accomplished are not well understood, it appears that there are two primary mechanisms: 1) steroids influence the function of neurons by binding to intracellular receptors regulating gene expression; and 2) they function as neuromodulators, affecting the activity of ligand-gated channels and of specific classes of receptors coupled to G-proteins (Kelly & Wagner, 1999; Levin, 1999; Rupprecht & Holsboer, 1999; Wagner et al., 2001). Estrogen in particular appears to have neuromodulatory effects at cholinergic, noradrenergic, serotonergic, and GABAergic synapses.

Much of the research to date has focused on estrogen, on its general effects on cognition (e.g., Steffens et al., 1999, used the Mini Mental State Exam), and possible role as a neuroprotectant in Alzheimer's disease (Henderson, 1997; Honjo et al., 1989; Ohkura et al., 1994). A number of studies, however, have focused on specific aspects of cognition, with a particular emphasis on verbal fluency, fine motor tasks, and learning and memory. For example, it has been found that pre-menopausal women, acting as their own controls, show superior verbal fluency and fine motor functioning when estrogen levels are higher (as in the midluteal phase of their cycle) than when they are lower. Post-menopausal women taking estrogen and women who are hypoestrogenic from taking GnRH agonists but taking "add-back" estrogen (Sherwin & Tulandi, 1996), compared with those not on estrogen, show similar results and experience beneficial effects on memory functioning (Baker et al., 2000; Hampson, 1990a, 1990b; Hampson & Kimura, 1988; Phillips & Sherwin, 1992;

Sherwin, 1988, 1999). Even among healthy young men, higher levels of estradiol were associated with superior performance on measures of visual memory (Kampen & Sherwin, 1996). Such results have been obtained even among women with Alzheimer's disease (Asthana et al., 1999a, 1999b, 1999c). Not all findings have been positive, however. For example, Barrett-Connor and Goodman-Gruen (1999) reported no relationship between endogenous estrogen level and any measure of cognition among a sample of older women not on hormone replacement therapy (although they also reported a relationship between higher levels of T and two cognitive measures), but in that study the assays were conducted on blood drawn several years prior to the cognitive assessment. Overall, the findings have generally been consistent.

The effects of androgens on cognition have been less well characterized, although there is evidence that T is important for certain aspects of cognition. The strongest support comes for the role of T on tasks involving a strong spatial component, such as judging line orientation or mentally rotating visual images (Janowsky et al., 1994; Kimura, 1999; Van Goozen et al., 1995). Testosterone levels vary during the course of the day and across seasons, and moderate, but not low or high levels of T, are associated with better performance on tests of spatial ability (Kimura & Hampson, 1994; Moffat & Hampson, 1996). A recent report (Janowsky et al., 2000) suggested that working memory for visual material was improved by T supplementation among healthy older men, although working memory was unaffected among older women given estrogen supplements. An earlier study of 33 young men (with T levels in the normal range), however, found T levels unrelated to memory performance. There have been no studies reported in the literature such as the one we propose here.

Given that: 1) sex steroids influence the performance of a number of different kinds of cognitive tasks; 2) these effects appear to be mediated by neuromodulation and gene expression in the brain; and 3) androgen blockade must necessarily disrupt the influence of both androgens and estrogens at the neuronal level, there is a compelling need to investigate the relationships among AD, sex steroid levels, and performance on tasks that have been shown to be influenced by the plasma level of either estrogens or androgens. Importantly, cognitive impairment has frequently been shown to be associated with poorer QOL (e.g., Lloyd et al., 2000; Moore et al., 2000; Schrag et al., 2000). This may be the case especially among older adults, for whom cognitive impairment may be associated with impaired performance of activities of daily living (ADL), instrumental ADLs, and reduced independence (Grigsby et al., 1998; Kaye et al., 1990). The proposed research thus is poised to contribute significantly to an understanding of an important factor affecting QOL among men with prostate cancer and to better illuminate the influence of androgens on specific aspects of cognition.

5. Investigators

Given the nature of this research project, it is important that the research team bring multidisciplinary expertise to the project. The varied contributions of the key investigators are as follows:

Jim Grigsby, PhD, (P.I.) is a cognitive neuroscientist and health services researcher at the University of Colorado Health Sciences Center (UCHSC), where he is Associate Professor in the Department of Medicine (Geriatrics), and Senior Researcher at the Center for Health Services Research (CHSR). With 25 years of experience in cognitive neuropsychology as a researcher and clinician, his research has focused on specific cognitive functions (especially executive cognitive abilities, information processing, and working memory) in several different populations. He has extensive experience with neuropsychological measurement, has played a leading role in several national, multi-site studies, and is familiar with a wide range of data analytic techniques.

L. Michael Glodé, MD, is the Robert Rifkin Professor for Prostate Cancer Research in the Medicine Department at the University of Colorado Cancer Center. His laboratory continues an active research program on the effects of GnRH analogues on prostate cancer in various model systems. He has two full days of clinic each week, seeing approximately four new cases of prostate cancer, and follows >200 active patients at any one time. In addition, he speaks to local prostate patient advocacy groups such as UsToo and Man to Man throughout the Denver and front-range area. He will be responsible for recruiting patients from these resources and from the collaborating physicians locally and nationally.

Peter W. Shaughnessy, PhD, is Director of CHSR and Professor of Medicine (Division of Geriatrics) at UCHSC. He is a mathematical statistician with over 30 years experience in research methods in health care research focusing on chronic and degenerative conditions and diseases in elderly populations. He has served as a P.I. and lead statistician on over 25 national, multi-year studies involving primary data collection on patients in hospital, clinic, and long-term care settings. As a prostate cancer patient who has personally undergone and researched the primary therapies discussed in this proposal, he brings to bear on this research the perspectives of a health care researcher, a patient, and a statistical scientist.

Sanjay Asthana, MD, is a geriatrician, a staff physician at the GRECC at the VA Puget Sound Health Care System, and Research Associate Professor in the Department of Medicine at the University of Washington School of Medicine. Dr. Asthana's research interests have emphasized the clinical psychopharmacology and neuroendocrinology of gonadal steroids and cholinergic drugs in Alzheimer's disease and healthy aging. He will serve as a consultant regarding psychoneuroendocrinology and will help in data analysis and reporting.

Angela G. Brega, PhD, is a Research Associate in the School of Medicine at UCHSC and Research Associate at CHSR. Dr. Brega holds a PhD in psychology and is experienced in all phases of research design; instrument development; data collection, management, and analysis; and project management. She will contribute to all aspects of this study and, in particular, will serve as Project Manager, with oversight for data collector training, data collection, and statistical analysis.

B. HYPOTHESES/RATIONALE/PURPOSE

1. Rationale

The major purpose of this study is to add significant new knowledge to the field of prostate cancer research and improve the QOL for men with this illness. We will examine cognitive functioning to elucidate the presence, nature, and severity of cognitive deficits among men undergoing AD therapy and to assess and quantify the relationship of any such deficits to plasma levels of sex steroids. Our hypotheses and specific aims are based on the premise that androgen blockade interferes with neuromodulatory processes and gene regulation that influence performance on specific cognitive tasks.

2. Hypotheses

The hypotheses associated with this major purpose are as follows:

a. Androgen deprivation therapy has a negative effect on cognitive functioning in men with prostate cancer. More specifically, this will be examined by testing the following two subhypotheses:
   1) Performance on selected measures of cognition will be worse for prostate cancer patients on AD than for subjects not on AD who have normal levels of T (this includes controls and off-treatment intermittent AD patients), after controlling for fatigue and depression.
   2) Patients on both continuous and intermittent, on-treatment, AD protocols will perform worse on cognitive measures than will age-matched healthy controls, after controlling for fatigue and depression.

b. Performance on working memory and visual-spatial tests will be associated with plasma T level.

c. Performance on verbal fluency and verbal learning and memory tests will be associated with plasma estradiol level.

d. Performance on tests previously not shown to be affected by sex steroid levels (e.g., verbal reasoning) will remain unaffected by AD.

e. Poor performance on measures of cognitive functioning will be correlated with poor QOL as measured by the SF-36.

Hypothesis *a* is the primary study hypothesis. To the extent that it is validated through empirical testing, the results of testing the remaining four hypotheses (*b* through *e*) will reveal further how and why the relationship in hypothesis *a* is effectuated.

C. OBJECTIVES

Specific Aims

To accomplish the overall goal described above and to guide us in testing our hypotheses, we propose the following specific aims. We intend to:

- assess whether there is evidence of cognitive impairment among patients on AD therapy;
- assess the nature and severity of that impairment, evaluating different aspects of cognition;
- use cognitive tests sensitive to fluctuations in levels of T or estrogen, and others that are unaffected by plasma sex steroid level, to evaluate whether the deficits observed are related directly to changes in the level of T, the level of estradiol, or of both;
- obtain plasma levels of T and estradiol at each data collection time point in order to evaluate the relationships between performance on specific cognitive tests and levels of these sex steroids; and
- examine the relationship between performance on cognitive measures and QOL.

D. METHODS

1. Overview

The research we propose will involve a prospective cohort study of prostate cancer patients receiving either continuous or intermittent CAD therapy. They will be compared with each other, and with a matched group of healthy control subjects, at each of three time points. In addition, within-subject performance of intermittent AD patients will be analyzed, using patients as their own controls, to determine whether AD is responsible for observed cognitive deficits. Each subject will be examined using a battery of cognitive tests and will be asked to give a blood sample on each occasion for measurement of T and estradiol levels.

This study will be conducted as a supplement to SWOG protocol 9346, which was discussed in the introduction to this application. In that study, following an initial induction phase involving eight courses (seven months) of CAD therapy, stage IV prostate cancer patients are randomized to one of two arms. Patients assigned to the first arm receive continuous CAD, even in the absence of disease progression (as determined by level of PSA). Individuals assigned to the second arm, following the induction phase, discontinue CAD therapy and are observed until either their PSA rises to approximately 20 ng/mL or they show clinical signs of disease activity. At that time, patients resume CAD for a second round of eight courses (seven months), after which time, if PSA is within normal limits, CAD is again discontinued. We propose to use patients already participating in both the intermittent and continuous arms of this SWOG protocol.

2. Recruiting

Subjects will be males aged 50 and older who meet the inclusion and exclusion criteria for the clinical trial. There will be two sources of participants with prostate cancer. First, CAD subjects will be recruited from centers participating in SWOG protocol 9346. We will recruit as many as possible from the University of Colorado Hospital, but will have access to patients being treated in other centers as well. Second, some participants will be enrolled who are not on the experimental protocol, but who are being treated by Dr. Glodé, who meet the inclusion and exclusion criteria and who are on intermittent or continuous AD. Healthy controls, matched on age (within five years) and education (within two years), will be recruited from the community. To minimize genetic and socioeconomic variance, we will first attempt to recruit brothers of patients who participate in the study. Control subjects also may be recruited from among the brothers of prostate cancer patients who participate in local support groups but who do not participate in the study. We have close contacts with several such groups. On the basis of power calculations (discussed below), we have determined that we will need approximately 22 subjects per group for mean comparisons with $\alpha = 0.05$, and 31 subjects per group if $\alpha = 0.01$. To deal with the likelihood of attrition due to mortality, exacerbation of prostate cancer, exacerbation of other chronic illnesses, development of new acute illnesses, and other factors that might affect this predominantly older sample, we plan to recruit 35 subjects per group.

3. Inclusion and Exclusion Criteria

All participants will be men aged 50 and older, fluent English speakers, and willing to provide informed consent for participation. They will conform to the inclusion and exclusion criteria for the CAD clinical trial. As these are quite detailed, they will only be summarized here.

- Adenocarcinoma of the prostate, with or without metastases to bone, brain, liver, or lung;
- Elevated PSA (5 ng/mL or greater);
- No concurrent biological response modifier therapy or chemotherapy; no concurrent hormonal therapy; and at least one year since any prior neoadjuvant or adjuvant hormonal therapy, or any prior finasteride;
- No concurrent radiotherapy other than palliation of painful bone metastases;
- No prior bilateral orchiectomy;
- No active medical illness precluding treatment or limiting survival;
- No second malignancy within five years except adequately treated nonmelanomatous skin cancer, in situ bladder cancer or other superficial cancer; and
- No history of neurologic disorder, head trauma with loss of consciousness, learning disability, mental retardation, history of alcoholism, or psychosis.

Controls will be healthy men aged 50 and above with no history of cancer chemotherapy, neurologic disorder, head trauma, learning disability, mental retardation, alcoholism, or psychosis. Because only adult men are affected, women and children are excluded. English-speaking minorities will be included in proportion to their representation in the clinical trial. The sample size is too small to permit meaningful ethnic comparisons.

4. Participating Sites

The primary data collection site will be the University of Colorado Hospital in Denver. Other sites participating in the Phase III trial may be used as well. The three most active SWOG, NCI, and ECOG sites have already enrolled a total of 253 patients, suggesting that we will have adequate numbers.

5. Consent Procedure

Consent will be obtained by an investigator thoroughly familiar with the clinical trial protocol. Consent will be sought in the clinic during a routine clinic appointment and the patient (or control) will be given time to consider the research and whether he wishes to participate. After receiving information on the study, he will be given an opportunity to ask any questions and inquiries will be made to determine whether he fully understands the requirements of participation and his rights as a subject. After signing an informed consent form, the subject will be given a copy of the consent and his consent will be documented in his clinic chart.

6. Data Collection Time Points

We will obtain baseline data on as many patients as possible. Since this is a supplement to a clinical trial, however, we may not have access to all patients before they have begun AD. However, the scientific literature on cognition and androgen levels strongly supports the assumption that adequate variation in androgen levels will occur for the intermittent AD group between on- and off-treatment periods. Comparing androgen levels and cognitive functioning scores of the intermittent AD group during the off-treatment period with the same variables for controls will provide an indication of whether AD may have a lasting effect on cognition beyond the period of blockade. In addition, because we will have blood hormone levels at each time point for each subject, we will be able to ensure the equivalence of the hormonal milieu, which is fundamental to our comparisons. Should there be variability across groups in this regard, we will use the actual levels, as well as number of on-treatment periods undergone and duration of those periods as covariates.

Patients on intermittent CAD will be administered cognitive tests: 1) at baseline (before beginning AD) if possible, or 12-16 weeks after discontinuation of androgen blockade; 2) 12-16 weeks following resumption of androgen blockade; and 3) 12-16 weeks after discontinuation of androgen blockade. Patients on continuous CAD also will be examined at three time points: 1) at baseline (before AD) if possible or after at least 12 weeks on AD; 2) after another 12-16 weeks of continuous AD; and 3) after another 12-16 weeks of AD. This design will allow comparison of the effect of CAD on cognition while controlling for practice effects. Control subjects

also will be administered the tests on three occasions: 1) at baseline; 2) after 12-16 weeks; and 3) after another 12-16 weeks. According to Akakura et al. (1993), serum T returns to the normal range within a median of about eight weeks (range 1-26 weeks) of stopping suppression, so that by waiting for three to four months after cessation of CAD, we can be fairly certain that serum T levels will be within normal limits for most participants even without assays. Nevertheless, we will obtain T and estradiol assays at each time point. Because it will not be possible to obtain any off-treatment data for some continuous CAD patients, the crucial repeated measures comparisons for them versus the other two groups will be at time points 2 and 3.

Examination at each of the three time points will require about 90 minutes. To minimize fatigue, there will be a break midway through administration and more frequently if needed. For those unable to complete the testing in one sitting, they will be tested over two sessions. Data collectors will be trained to evaluate fatigue and asked to reschedule testing if fatigue appears to affect performance. To prevent unanticipated order effects in the cognitive assessment, the order of administration of tests will be randomized across subjects. To minimize circadian variability in performance (Blake, 1967), subjects will be scheduled for assessment at the time of day they prefer and these assignments will remain constant for each subject across time points.

7. Cognitive and Neuropsychologic Instruments

Following are the measures to be administered in this study, accompanied by brief discussion of their properties. Performance on certain of these has been shown to be dependent on level of T, of estrogen, or neither. Because T is converted into estradiol via aromatization, it is possible that cognitive effects observed as a result of T suppression could be a result of low levels of either of these hormones.

a. Working Memory

Working memory (Baddeley, 1990; short-term storage of information upon which cognitive operations simultaneously must be performed, or which is needed for performance of concurrent tasks) is often impaired among older adults (Raz, 2000). Among older men, working memory has been shown to be sensitive to T level (Janowsky et al., 2000). The following will be used as measures of working memory and immediate recall.

Letter Number Sequencing: A subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) in which subjects are presented with mixed sequences of letters and numbers (e.g., 3-e-7-9-p), then must separate letters and numbers and repeat them in the proper sequence (e.g., 3-7-9-e-p). The test is a reliable and valid measure of verbal auditory working memory (Wechsler, 1997).

Visual Working Memory: This test involves recall of a set of abstract drawings presented in groups of 6, 8, 10, or 12, in different spatial arrangements on separate cards. Shown each card one at a time, the subject must touch a picture not previously touched in a series. An error occurs when the subject touches a card previously touched in that set (Petrides & Milner, 1982). This test was previously used by Janowsky and associates (2000) in their study showing that T affected working memory.

b. Speed and Capacity of Information Processing

Performance on most tasks is influenced by one's speed and capacity for processing information. Although these abilities have not typically been found to be associated with sex steroid levels (but see Asthana, 1999c), they are sensitive to depression and fatigue. The following are considered direct measures of these abilities.

Symbol Digit Modalities Test (SDMT): This is a measure of processing speed (Smith, 1968). Similar to the Digit Symbol subtest of the WAIS-III, the subject is required to provide the number associated with each of nine different symbols. Scores are based on the number of correct responses in a 90-second trial. Reliability is very good. Performance on the SDMT has been shown to be associated with a number of neurologic conditions, and with the P3 component of evoked potentials (Spreen & Strauss, 1998).

Grammatical Reasoning: An experimental measure of simple reasoning sensitive to deficits in speed and capacity of information processing (Baddeley, 1968), it consists of 32 simple declarative statements having systematic variations in grammatical construction (e.g., "A is followed by B," "B is not preceded by A"). Each is followed by the letters **AB** or **BA**. The subject must say whether each statement about the letters is true or false. The subject's score is the number of items answered correctly in three minutes.

c. Declarative Verbal Learning and Memory

Among women and men, verbal learning and memory have been found to be sensitive to estrogen level. The influence of estrogen in men is less clear than in women, but performance on the following tests might well be influenced by absence of estradiol. It might also be influenced by deficits in working memory.

Logical Memory Subtest of the Wechsler Memory Scale-III (WMS-III): A test of declarative verbal memory, involving immediate and 30-minute delayed recall for two short paragraphs read to the subject by the examiner (Wechsler, 1997). Interrater and test-retest reliabilities are > 0.90 (Wechsler, 1997). We will use only one of the two paragraphs at each time point. For repeat testing, we will use the second paragraph and equivalent paragraphs from the second edition of the WMS (Wechsler Memory Scale-Revised).

Rey Auditory Verbal Learning Test (RAVLT): A brief, easily administered auditory verbal learning test comprised of 15 unrelated concrete nouns repeated for five trials. Recall is requested after each presentation of the words. After the fifth trial, a second interference list is read to the subject, and after a 20-minute delay, both recall and recognition are tested for the first list. The scores of interest are the number of words correctly recalled after the first presentation, the number recalled by the fifth trial, the number of words recalled after 20 minutes, and 20-minute recognition. Different, parallel forms of the test are available for retesting.

d. Verbal Reasoning

Verbal reasoning has not been shown to be affected by sex steroid levels. It may serve as an important covariate in analyzing data from other cognitive tests. These tests will be administered to provide an estimate of verbal intellectual level and to determine whether performance on them is influenced by T level.

Similarities and Vocabulary Subtests of the WAIS-III: The Similarities and Vocabulary subtests (Wechsler, 1997) will be used to assess general verbal reasoning ability. These are relatively independent of memory and are highly correlated with the Wechsler verbal IQ score. We anticipate little change in either score and intend to use these subtests primarily to control for verbal intelligence.

e. Verbal Fluency

Tests of verbal fluency have been shown to be sensitive to estrogen level in women. Whether, and to what extent, they are affected by sex steroids in men is unknown.

Controlled Oral Word Association Test (COWAT): Commonly described as a test of verbal fluency or cognitive flexibility, the COWAT reflects the ability to generate information actively and is correlated strongly with measures of executive functioning. Over three trials, the subject must say as many words as he can think of in a 60-second period, starting with a given letter (F, A, and S). Reliabilities are very good to excellent (ranging from 0.70 to nearly 1.0; desRosiers & Kavanagh, 1987; Spreen & Benton, 1977).

f. Spatial Perception

Performance on tests of spatial perception has been found to be associated with T level. Among men, even relatively subtle variations in the level of this sex steroid may affect performance either positively or negatively. We will use the following tests.

Vandenberg and Kuse Mental Rotation Test: This consists of a number of line drawings of three-dimensional geometric objects (Vandenberg & Kuse, 1978). A stimulus figure is compared with four variations on this figure, one of which is identical to the stimulus figure except that it is drawn so it is rotated. The subject must select the identical rotated figure. This is the most commonly used test of mental rotation.

Benton Line Orientation Test: Two lines at different angles relative to the horizontal are presented on a card and the subject's task is to identify, on a second card, which of 12 different lines' angles match these. This test is a valid and reliable measure (Benton et al., 1983).

g. Depression

Depression and fatigue may affect performance on a number of the tests discussed above entirely independently of the influence of sex steroids or other factors. We, therefore, will collect data on these variables as covariates in the analysis. Depression will be evaluated using the Center for Epidemiologic Studies Depression

Scale (CES-D; Radloff, 1977). This scale contains fewer items that might reflect physical disability than do other depression scales and has been demonstrated to be a reliable and valid measure of depression.

h. Quality of Life and Fatigue

Quality of life will be assessed using the SF-36, a general health status instrument used in the RAND Medical Outcomes Study (Ware & Sherbourne, 1992). The scale is reliable and valid as a measure of QOL (e.g., Andresen & Meyers, 2000; Lloyd et al., 2000). Scores on the fatigue subscale will be used to control for the effects of fatigue on performance. Subjects also will be asked to rate level of fatigue at each time point on a 10-point analog scale, noting current fatigue and average for the past week.

8. Hormone Assays

Blood will be drawn each time a patient is examined in order to conduct assays for T and estradiol (both free and bound). Samples will be analyzed at the UCHSC General Clinical Research Center. This will permit us to ensure the equivalency of subjects' hormonal milieux and to adjust statistically for differences if there is variability in sex steroid level in suppressed or non-suppressed states.

9. Training and Quality Control of Data Collectors

Data collectors at each center will be responsible for enrolling subjects and administering all instruments. Data collectors will be trained face-to-face by either Dr. Brega or Dr. Grigsby in the administration of each test. Data collectors will then administer complete sets of the tests on three occasions to persons who are not study participants. At least two of these administrations will be observed directly, videotaped, or observed via videoconference. Differences or problems in administration and scoring will be discussed and reconciled between observers and data collectors. For each data collector, the first three actual assessments of participants will be observed by video as well, and feedback given to the data collectors. After each data collector has completed 10-12 patient exams, she or he will again be observed by the investigators. We will conduct an interrater reliability analysis using 15 videotaped assessments of participants. Dr. Brega will be responsible for ensuring the accuracy of scoring. After a data collector has completed a total of 10-15 patient assessments, she or he will be observed again by the investigators.

10. Data Analysis

All data management and analysis will be conducted at CHSR under the supervision of Drs. Brega and Grigsby. Data will be double-entered to ensure quality control, with discrepancies resolved by review of original data forms. We will use SPSS and SAS for analysis.

To evaluate data integrity and completeness and to characterize the samples within each group, frequency distributions and descriptive statistics will be obtained. We then will assess mean differences among the groups on clinical and demographic factors. The overall analytic plan will include modeling cognitive functioning, using both mean differences (between continuous variables) and percent of persons classified as impaired (for dichotomous variables). Comparisons will be made over time and across the three patient cohorts included in this study. For continuous measures of cognition, repeated measures analysis of covariance (ANCOVA) and multivariate analysis of covariance (MANCOVA) will be used. An advantage of MANCOVA with the cognitive tests is that it limits the number of mean comparisons, hence avoiding inflation in experiment-wise Type I error rate. For example, MANCOVA might be used to examine working memory, with each test score as a dependent variable, treatment group as a fixed independent variable indicating on- or off-treatment status, and fatigue, depression, and T level as covariates. When multiple comparisons are made, we will use the Holm method (as opposed to those of Bonferroni or Dunn) of correction (Aickin & Gensler, 1996; Holm, 1979). For dichotomous measures, logistic regression models will be applied. We also will use multiple regression to assess the contribution of a number of different variables to specific dependent variables. Such variables as age, education, depression, comorbidity, verbal reasoning, and hormonal status may be included as covariates. In addition to these analyses, there are opportunities to profile patients at greatest risk of cognitive impairment (on variables such as age, education, comorbidity) using the approaches described above.

11. Statistical Power and Sample Size Estimates

The projected sample size of 35 patients per group was determined by estimating statistical power, then adding to the total in order to deal with possible problems resulting from attrition. We anticipate adequate power to detect small-to-moderate differences over time, as well as among the three groups. We estimated necessary sample sizes to obtain power using repeated measures analysis of variance (ANOVA) with three conditions and a total of three measures per subject. Based on cognitive research in other contexts, we assumed an effect size of 0.4, which is about midway between what Cohen (1973) considered small (0.25) and medium (0.5) effect sizes. With this effect size, at $\alpha = 0.05$, 22 subjects are required to achieve power $(1-\beta) = 0.80$. At $\alpha = 0.01$, it would require 31 subjects to achieve $1-\beta = 0.80$.

12. Limitations of the Study

This proposed study has certain limitations, which we have addressed in the following ways. First, because of its dependence on subjects obtained primarily from a SWOG protocol, recruitment of an adequate local sample could be slow. We, therefore, will recruit patients from sites other than the University of Colorado Hospital. Second, because this is an ancillary study associated with a clinical trial, the clinical needs of patients always take precedence and it may, at times, not be possible to examine participants at a scheduled second or third visit. Intermittent CAD patients, for example, may need to resume androgen blockade in response to changes in their clinical condition. This is one of the reasons for sampling more patients than power calculations suggest are necessary. Third, despite the use of hormone assays and the use of tests sensitive to changes in the level of specific sex steroids, it may be difficult to draw conclusions about the unique effects of either T or estrogen on specific aspects of cognition. We may only be able to analyze correlations between test performance and sex steroid levels and perhaps draw inferences about the effect of the androgen blockade itself. Fourth, because of the limited sampling frame, we will need to enroll an unknown number of subjects who are already on an AD protocol and, therefore, will be unable to obtain pre-therapy baseline measures on some of the prostate cancer patients. However, the scientific literature on cognition and androgen levels strongly supports the assumption that adequate variation in androgen levels (and cognitive functioning, to the extent that our primary hypothesis is correct) will occur for the intermittent AD group between on- and off-treatment periods. Comparing the androgen levels and cognitive functioning scores of the intermittent AD group during the off-treatment period with the same variables for the control group will provide an initial indication of whether AD may have a lasting effect on cognitive functioning beyond the period of its direct administration. In addition, because we will have blood hormone levels at each time point for each subject, we will be able to ensure the equivalence of the hormonal milieu. Should there be variability across groups in this regard, we will be able to use the actual levels, as well as number of on-treatment periods undergone, and duration of those periods, as covariates.

13. Summary

The research we propose is highly responsive to the research priorities of the Department of Defense CDMRP Prostate Cancer Research Program. In particular, the proposed study, which is based on a sound rationale and a well-established body of literature on sex steroids and cognition--would contribute to improvement in "the quality of life for individuals and their families living with prostate cancer" by addressing a previously neglected issue: the effects on cognition of hormone therapy for prostate cancer. This represents innovative research on an important side effect of hormone therapy, regarding which there are no previous data. Hence, the New Investigator Award is an ideal vehicle for such a study. The Principal Investigator is experienced in the assessment of cognitive deficits in a number of populations--especially older adults, who will be the primary target of this study--and has some experience with the cognitive effects of breast cancer treatment, but has not conducted research in the field of prostate cancer. The research team is staffed with personnel highly skilled in medical oncology, sex steroid research, neurocognitive assessment, and the conduct of large-scale research projects. In short, this is a new and undeveloped, yet very important area of investigation that would benefit greatly from this proposed study.

Statement of Work

Task 1: Finalize study protocols and preparation for data collection (months 1-3).

a. Prepare study brochure and consent form describing study for patients (month 1)
b. Prepare written protocols for recruitment, data collection, and data management (months 1-2)
c. Recruit and train data collectors (months 1-3)
d. Prepare data collection instruments (months 1-2)
e. Prepare database (months 1-3)

Task 2: Conduct of study (months 3-30).

a. Begin subject recruitment and data collection (month 3)
b. Begin first follow-up data collection [time point 2] (month 6)
c. Subject recruitment completed (month 26)
d. Time point 3 follow-up data collection completed (month 32)

Task 3: Interim data analysis (months 24-30).

a. Preliminary data edits and transformations (months 24-27)
b. Preliminary descriptive analyses (months 27-30)

Task 4: Annual reports.

a. Prepare annual report for year 01 (months 11-12)
b. Prepare annual report for year 02 (months 23-24)

Task 5: Final data analysis and report preparation (months 28-36).

a. Specification of final data analyses (months 28-31)
b. Conduct final data analyses (months 32-34)
c. Write articles and submit for publication (months 28-36)
d. Write final report (months 34-36)

APPENDIX B

ANNUAL REPORT: STUDY YEAR 1

This appendix contains the body of the report for Study Year 1, and is included for reference.

ANNUAL REPORT FOR AWARD NUMBER DAMD17-02-1-0040

Cognitive Functioning Among Men with Stage IV Prostate Cancer Undergoing Combined Androgen Deprivation (CAD) Therapy

Introduction

Hormonal treatment of prostate cancer by means of androgen deprivation (AD) can be an effective means of inducing tumor regression and delaying progression of the disease. The treatment, however, adversely affects quality of life (QOL), causing fatigue, depression, impotence, and loss of libido. Anecdotal evidence suggests that cognitive function also may be negatively affected. Because men with prostate cancer may survive for many years if the disease is suppressed, the identification of possible negative influences of life-prolonging treatment on their QOL, and the development of means to treat them, is of great importance. The research questions we are investigating address the relationship between sex steroid levels and different aspects of cognitive functioning. Our specific aims are to: 1) assess whether there is evidence of cognitive impairment among patients on AD therapy; 2) assess the nature and severity of that impairment; 3) determine whether any cognitive deficits observed are related to T suppression, decreased estrogen level, or both; 4) evaluate the relationships between performance on specific cognitive tests and levels of certain sex steroids; and 5) examine the relationship among performance on cognitive measures, steroid levels, and QOL. We are examining men on continuous AD, a matched sample of men on intermittent AD, and a matched sample of healthy controls using tests of working memory, learning, verbal fluency, spatial perception, and verbal reasoning. Each subject is tested at three time points, approximately four months apart. We obtain T and estrogen levels, evaluate cognition, and assess QOL at each timepoint.

Body of Report

This project has been hampered by numerous delays related to institutional approvals and issues with the Health Insurance Privacy and Portability Act of 1996 (HIPAA). As noted in the original statement of work (Appendix A), we had anticipated that data collection would begin by the fourth study month. In fact, we only began subject recruitment in the final quarter of calendar year 2002. This delay was a result of requirements imposed by several layers of bureaucracy at the University of Colorado Health Sciences Center (UCHSC) related to human subjects research and to the use of the resources of the University's General Clinical Research Center (GCRC). A chronology of events follows.

We received a memorandum from the Adriene D. King, Ph.D, Human Subjects Protection Specialist with AMDEX Corporation, dated 17 December 2001 requesting minor revisions to the consent form and protocol (Appendix B, page 4). We submitted these revisions to the Colorado Multiple Institutional Review Board (COMIRB) from which we received approval on 11 February 2002 (Protocol Update and Protocol Amendment in Appendix C).

Assuming that we could begin recruitment expeditiously, we submitted a recruitment flyer to COMIRB and received approval from COMIRB on 4 February 2002. This flyer was subsequently distributed at an educational conference, held at the UCHSC, for men with prostate cancer. We received several calls in response from persons interested in serving as research participants, and they were added to a tracking database.

We had planned to use the resources of the GCRC in order to pay for a number of hormone assays. The University's GCRC is funded by the National Institutes of Health to support research studies, covering expenses that otherwise would need to be charged as direct costs to research grants. We learned that because the GCRC is located physically at University of Colorado Hospital, it was therefore necessary to seek the approval of the Hospital Research Resources Committee (HRRC) for the research. We submitted an application to the HRRC on 4 February 2002 (Appendix D), and it was tentatively approved on 27 February 2002, pending approval by the GCRC (Appendix E).

The GCRC meets monthly, and we submitted our application to the Center for review on 1 April 2002. In late April, we received a summary of the comments of the Scientific Advisory Committee (SAC) of the GCRC dated 4 April 2002 (Appendix F). The SAC had a large number of comments which needed to be addressed before approval would be given for the study. A serious illness and subsequent death in my family made it impossible to respond immediately, but on 30 August 2002 I submitted a detailed response to the SAC's critique of the project (Appendix G).

The SAC did not respond until 9 October 2002, at which time they continued to express reservations about the protocol and the assays we were requesting, although they had agreed with all the other points in my response of 30 August (Appendix H). On 14 October 2002, I responded to the SAC (Appendix I), and we received final approval from the GCRC on 31 October 2002 (Appendix J).

On 7 November 2002 we notified the HRRC that we had finally obtained GCRC approval to conduct the study (Appendix K). The HRRC then notified us that all study research personnel having contact with patients would have to go through the Hospital's credentialing process, including purified protein derivative (TB) testing. This was completed, and we received HRRC approval.

A required meeting of the investigators (Grigsby and Glodé) with GCRC clinical and administrative staff was scheduled for mid-December, at which time arrangements were made for use of the GCRC facilities, and lines of communication were established.

We once again began recruiting, and the use of a new flyer and an advertisement letter for eligible patients necessitated COMIRB approval once again. In addition, because the GCRC refused to pay for assays conducted using blood from patients not enrolled at the GCRC, we revised our plans for recruitment to include patients from Western Urologic Research Center, in Wheat Ridge, Colorado. This is a large specialty private practice in the Denver area which has the potential to refer a sizeable number of patients who can be enrolled at the GCRC. However, addition of this site as a source of patients required a protocol update approval by COMIRB. This was first submitted to COMIRB on 8 January 2003 (Appendix L), and they requested additional paperwork on 16 January (which we received on 21 January 2003, Appendix M). We are in the process of submitting an updated protocol amendment (Appendix N), and when approval has been obtained we will in turn submit notification to the Department of Defense IRB.

Finally, on 22 January 2003, we were notified that we must obtain the approval of the University of Colorado Hospital Cancer Center Protocol Review Committee, and we are in the process of preparing that application. Once final approvals are obtained, we already have a preliminary list of eligible subjects. Data collection is ready to begin, and we can start immediately.

Key Research Accomplishments

There are no substantive research accomplishments to report. We have dealt with various regulatory committees, a process that is now nearly complete. Arrangements have been made with the GCRC to begin data collection as soon as all necessary approvals have been obtained. Data collectors have been trained, and both a participant tracking database and a database for entry of participant data have been developed and debugged.

Reportable Outcomes

None to report.

Conclusions

None to report.

APPENDIX C

UCHSC CANCER CENTER APPROVAL

This appendix contains the approval form from the application submitted to the University of Colorado Cancer Center's Protocol Review & Monitoring Committee. Approval was received July 2, 2003.

UNIVERSITY OF COLORADO CANCER CENTER
PROTOCOL REVIEW & MONITORING COMMITTEE

DATE: July 2, 2003

TO: Jim Grigsby, PhD
C-241

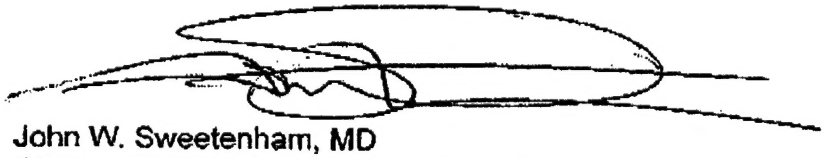
FROM: UCCC Protocol Review & Monitoring Committee

PROJECT TITLE: UCCC #03-100, Effects of Androgen Blockade on Cognitive Function and Quality of Life in Men with Prostate Cancer (DOD PC010257) (COMIRB #02-522

The above-submitted protocol has been reviewed for scientific merit and protocol design. It was approved as a Cancer Center trial on July 2, 2003. As a result of this approval, the protocol will be made available to all clinical investigators of the University of Colorado Cancer Center. Quality assurance monitoring will be done through periodic review of patient accrual statistics, yearly review of patient and study summaries, and at the time of a reported Adverse Event (AE).

Please note: All projects approved by this committee must be submitted to COMIRB and any participating hospitals' IRB/Human Subjects Committee (as appropriate) for review and approval prior to study activation.

Any questions regarding this committee action should be directed to the Clinical Investigations Core Protocol Review & Monitoring Committee office at Box F-700 or call (720) 848-0391



John W. Sweetenham, MD
Chair, UCCC Protocol Review Committee

cc: Patricia DeVore